ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 20.e19–20.e22

UROLOGIC ONCOLOGY

Original article

Dermatological exposure to coal tar and bladder cancer risk: A case-control study

Judith H.J. Roelofzen, Ph.D.[a], Katja K.H. Aben, Ph.D.[b,c], Peter C.M. Van de Kerkhof, M.D., Ph.D.[d], Pieter G.M. Van der Valk, Ph.D.[e], Lambertus A.L.M. Kiemeney, Ph.D.[b,c,f,*]

[a] *Department of Dermatology, Koningin Beatrix Hospital, Winterswijk, the Netherlands*
[b] *Department for Health Evidence, Radboud University Medical Centre, Nijmegen, the Netherlands*
[c] *Department of Registry and Research, Comprehensive Cancer Centre The Netherlands, Utrecht, the Netherlands*
[d] *Department of Dermatology, Radboud University Medical Centre, Nijmegen, the Netherlands*
[e] *Department of Dermatology, van Weel-Bethesda Hospital, Hellevoetsluis, the Netherlands*
[f] *Department of Urology, Radboud University Medical Centre, Nijmegen, the Netherlands*

Received 12 September 2013; received in revised form 13 December 2013; accepted 15 December 2013

Abstract

Objective: Coal tar ointments are used as treatment of various skin diseases, especially psoriasis and eczema. These ointments contain several carcinogenic polycyclic aromatic hydrocarbons. Metabolites of these polycyclic aromatic hydrocarbons are excreted in the urine and therefore, dermatological use of coal tar may be associated with an increased risk of bladder cancer. The objective of this study was to evaluate the association between dermatological use of coal tar ointments and bladder cancer.

Material and methods: A population-based case-control study was conducted including 1,387 cases diagnosed with bladder cancer and 5,182 population controls. Information on the use of coal tar, history of skin disease, and known risk factors for bladder cancer was obtained through postal questionnaires. Logistic regression analyses were performed to estimate the risk of bladder cancer after coal tar treatment, adjusted for age, gender, smoking status, duration of smoking, and intensity of smoking.

Results: The use of coal tar ointments was approximately equal among cases and controls (3.8% vs. 3.0%, respectively). Dermatological application of coal tar was not significantly associated with bladder cancer (adjusted odds ratio = 1.37, 95% CI: 0.93–2.01). An inverse association between bladder cancer and a history of skin disease was observed (adjusted odds ratio = 0.74, 95% CI: 0.61–0.90).

Conclusion: This is the first study with a specific aim to study the association between the use of coal tar preparations and bladder cancer. The results suggest that there is no reason for safety concerns with respect to the risk of bladder cancer after the use of coal tar preparations in dermatological practice.

Keywords: Coal tar; Polycyclic aromatic hydrocarbons; Bladder cancer; Psoriasis; Eczema; Case-control

1. Introduction

Coal tar is an effective therapy in the treatment of chronic skin diseases, such as psoriasis and eczema [1]. It contains more than 10,000 compounds, including polycyclic aromatic hydrocarbons (PAHs), in high concentrations. Some PAH, such as benzo(a)pyrene are classified as human carcinogens [2,3]. Because of the carcinogenic potency of PAHs, concerns have been raised about the risk of cancer after coal tar treatment in patients with skin diseases. The skin is an important route of uptake after dermatological exposure to coal tar [4]. Several studies have therefore investigated the risk of skin cancer after coal tar treatment but most studies [5–8], except one of Stern et al. [9], did not observe an increased risk. After application, coal tar is absorbed and metabolized in the skin and body. After metabolization, several metabolites of PAHs are excreted in the urine [10]. Therefore, dermatological use of coal tar might be associated with an increased risk of nonskin cancer, especially bladder cancer. The risk of nonskin cancer in patients treated with coal tar was investigated in only a few studies and most of these studies did not observe an increased risk of internal malignancies [6,11–13]. However, none of the previously performed studies had a specific aim to test the association between bladder cancer

* Corresponding author. Tel.: +31-24-3613745; fax: +31-24-3613505.
E-mail address: Bart.Kiemeney@radboudumc.nl (L.A.L.M. Kiemeney).

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.12.006

and dermatological application of coal tar preparations. In this case-control study, we examined the risk of bladder cancer after exposure to coal tar ointments used in the dermatological practice.

2. Material and methods

2.1. Study population and data collection

Patients were identified by the Department of Registry and Research of the Comprehensive Cancer Centre, Nijmegen, the Netherlands. All patients with bladder cancer who were diagnosed between 1995 and 2006, younger than 75 years, in this region, and alive at time of data collection were invited to participate in a study on genetic susceptibility and environmental risk factors for bladder cancer [14]. Patients filled out a detailed postal questionnaire concerning topics such as demographic factors, life style, history of diseases (e.g., cancer), and medication use. The response rate was 62%. For the current study, only bladder cancer cases with urothelial cell carcinoma were included ($n = 1{,}501$). Patients with missing data on skin disease, smoking status, or use of coal tar ointments were excluded ($n = 114$). A total of 1,387 cases were included in the analyses.

Controls were obtained through the Nijmegen Biomedical Study, a population-based survey conducted by the Radboud University Medical Centre in 2002 [15]. A random selection of inhabitants of Nijmegen were invited to participate in a study on risk factors for (any) disease by filling out a detailed postal questionnaire. In 2008, an additional questionnaire, more specifically aimed at potential risk factors for bladder cancer was sent to all participants of the Nijmegen Biomedical Study who gave consent for further research and were still alive then. A total of 5,613 (64%) persons returned this second questionnaire. Persons who were diagnosed with cancer (except for basal cell carcinomas of the skin) at the time of data collection were excluded ($n = 303$), as well as controls with missing data on smoking status and skin disease ($n = 128$). Coal tar exposure was measured as "yes" vs. "no." People with missing data on this variable ($n = 1{,}481$) were included in this category as well (assuming that persons who did not answer yes to this question did not use these preparations). A total of 5,182 controls were included in the analyses. All patients and controls gave written informed consent. The study was approved by the Institutional Review Board of the Radboud University Medical Centre.

2.2. Statistical analysis

Descriptive analyses were performed to provide insight into the characteristics of the patients and controls. Logistic regression analyses were performed to estimate odds ratios (ORs) and 95% CI for the association between the use of coal tar ointments and bladder cancer. These analyses were adjusted for age at completion of the questionnaire, gender, and smoking. Smoking and male gender are strong risk factors for bladder cancer. To exclude the effect of smoking in the association between coal tar and bladder cancer, subanalyses in nonsmokers were performed. In addition, subanalyses in men and women were performed. We also analyzed the association between occurrence of skin disease and bladder cancer because coal tar ointments are applied in patients with skin diseases. Models were not adjusted for height, weight, use of temporary or permanent hair dyes or both, and educational level because these variables did not alter the effect estimates in the models. All statistical analyses were performed in SAS (SAS system for Windows, version 9.2, SAS institute, Cary, NC).

3. Results

This study included 1,387 patients and 5,182 controls (Table 1). Patients were older at the time of completing the questionnaire compared with controls (67 y vs. 57 y). Smoking, both current and former, was more frequent in patients. Among current and former smokers, the patients had smoked for a longer period of time and the intensity of smoking was higher. Education level among patients was lower compared with controls. The use of coal tar ointments was approximately equal in both groups (3.8% vs. 3.0%). Among individuals exposed to coal tar, skin diseases were

Table 1
Characteristics of the study population

	Cases ($n = 1{,}387$)	Controls ($n = 5{,}182$)
Age at completion of the questionnaire, y[a]	67.3 ± 9.4	57 ± 16
Gender (% men)	84	46
Smoking status		
Never smokers, %	10.7	36.2
Former smokers, %	64.9	47.6
Number of cigarettes, cigarettes/d[a]	15.4 ± 4.5	12.6 ± 8.7
Smoking duration, y[a]	29.2 ± 13.7	20.4 ± 13.6
Age at start smoking, y[a]	17.5 ± 4.5	17.7 ± 4.6
Current smokers, %	24.4	16.2
Number of cigarettes, cigarettes/d[a]	15.3 ± 5.1	13.7 ± 8.1
Smoking duration, y[a]	42.7 ± 13.1	32.1 ± 15.2
Age at start of smoking, y[a]	17.6 ± 5.1	17.4 ± 5.0
Educational level, %		
Primary school	15.9	7.2
Technical/professional school	52	53.1
Secondary school	22.3	21.9
University degree	9.8	17.8
Use of temporary or permanent dyes or both, %	13.9	44.9
Skin disease, %	14.4	18.8
Use of coal tar ointments, %	3.8	3.0

[a]Mean ± standard deviation.

Table 2
Risk of bladder cancer associated with use of coal tar ointments and occurrence of skin disease

	Coal tar	Skin disease
	OR (95% CI)	OR (95% CI)
All[a]	1.37 (0.93–2.01)	0.74 (0.61–0.90)
Gender[b]		
Male	1.32 (0.85–2.05)	0.68 (0.54–0.85)
Female	1.57 (0.72–3.39)	1.05 (0.70–1.58)
Never smokers[c]	1.20 (0.41–3.53)	1.08 (0.68–1.72)

[a]OR were adjusted for age at completing the questionnaire, gender, smoking status, duration of smoking (in y), and intensity of smoking (cigarettes/d).
[b]OR were adjusted for age at completing the questionnaire, smoking status, duration of smoking (in y), and intensity of smoking (cigarettes/d).
[c]OR were adjusted for age at completing the questionnaire and gender.

more prevalent compared with the individuals who were not exposed (94% vs. 16.4%) (data not shown).

The risk of bladder cancer associated with exposure to coal tar ointments is presented in Table 2. The use of coal tar was not significantly associated with bladder cancer (OR = 1.37, 95% CI = 0.93–2.01). The strength of the association was comparable among men and women. The OR in the subgroup of nonsmokers was comparable to the total group (OR = 1.20 vs. 1.37), but this result was based on small numbers (n = 4 nonsmoking cases).

An inverse association between skin disease and bladder cancer was observed (OR = 0.74, 95% CI = 0.61–0.90) (Table 2), although this inverse association was restricted to men (OR men = 0.68, 95% CI: 0.54–0.85; OR women = 1.05, 95% CI: 0.70–1.58).

4. Discussion

This is the first population-based case-control study specifically aimed at assessing the risk of bladder cancer after dermatological use of coal tar. No association between dermatological exposure to coal tar and bladder cancer was observed. Several studies have shown that occupational exposure to PAHs is associated with an increased risk of bladder cancer [2,3,16]. The increased bladder cancer risk in occupational studies was observed in workers with prolonged occupational exposure, whereas dermatological use of coal tar is most often limited to a much shorter duration of exposure [10,17]. The results from the present case-control study are in accordance with the results found in some other studies, although these studies did not specifically address the risk of bladder cancer [6,11–13]. Differences in cancer risks between occupational studies and studies in patients may be explained by the duration of PAH exposure. Possibly, the body is capable of repairing tissue damage following short-term exposure to PAH but not to the same extent after long-term exposure.

We also investigated the association between bladder cancer and skin diseases. An inverse association between the occurrence of skin disease and bladder cancer was observed, although it was restricted to men. It is difficult to explain this observed association because no information on the type of skin disease was available from the questionnaires. However, it can be assumed that the major part of the reported skin diseases will be eczema followed by psoriasis. In both skin diseases, a hyperreactive immune system leads to chronic inflammation. In eczema, it has been hypothesized that this hyperreactive state may lead to increased tumor immunosurveillance, which may decrease the probability of proliferation of aberrant cells and therefore decreases the probability to develop malignancies [18,19]. Several studies have evaluated the risk of bladder cancer in patients with psoriasis or eczema, but they showed conflicting results [5,6,20–22]. Several patients in these studies had been treated with systemic therapies and as a result, it is not possible to exclude the effect of these therapies on the risk of cancer. In future research, it is worthwhile to only include patients with 1 type of skin disease to study the association between skin disease and bladder cancer.

It is known that cigarette smoking is the most important risk factor for bladder cancer [23]. In our study, detailed information on smoking (duration of smoking and intensity of smoking) was collected from the questionnaires and therefore we were able to adjust for smoking in our analyses. Another important risk factor for bladder cancer is occupational exposure to specific chemical substances, such as aromatic amines and PAHs [23]. Data on the occupational history of all patients and controls were not readily available and as a consequence our regression models were not adjusted for occupational exposure.

Information was assessed after the diagnosis of bladder cancer and therefore, recall bias cannot be excluded. We assume that recall is limited because questions on these topics were part of a questionnaire with a wide spectrum of questions and we have no reason to assume that patients or controls associate the use of coal tar or occurrence of skin disease with the development of bladder cancer. No information on the type and duration of coal tar preparations was asked in the questionnaires. In dermatological practice pix lithantracis and liquor carbonis detergens are used. Pix lithantracis contains far more PAHs than liquor carbonis detergens. In a large cohort study on the risk of cancer after coal tar treatment that we conducted previously, no differences in cancer risk were observed between the use of pix lithantracis and liquor carbonis detergens [13]. In the present study, it was not possible to confirm these results because information on the type of coal tar preparations was not collected.

We conclude that there is no reason for safety concerns with respect to the risk of bladder cancer after the use of coal tar preparations in dermatological practice.

References

[1] Roelofzen JHJ, Khawar AJM, Aben KKH, et al. Treatment policy of psoriasis and eczema by Dutch and Flemish dermatologists. Neth J Dermatol Venereol 2005;15:231–4.

[2] Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 1997;8:444–72.

[3] IARC. Polynuclear aromatic compounds, Part 4, Bitumens, coal-tars and derived products, shale-oils and soots. 35th ed. Lyon, France; 1985. p. 83–159.

[4] Van Rooij JG, Van Lieshout EM, Bodelier-Bade MM, et al. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. Scand J Work Environ Health 1993;19:200–7.

[5] Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol 2001;117:1531–7.

[6] Hannuksela-Svahn A, Pukkala E, Laara E, et al. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol 2000;114:587–90.

[7] Maughan WZ, Muller SA, Perry HO, et al. Incidence of skin cancers in patients with atopic dermatitis treated with coal tar. A 25-year follow-up study. J Am Acad Dermatol 1980;3:612–5.

[8] Pittelkow MR, Perry HO, Muller SA, et al. Skin cancer in patients with psoriasis treated with coal tar. A 25-year follow-up study. Arch Dermatol 1981;117:465–8.

[9] Stern RS, Zierler S, Parrish JA. Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. Lancet 1980;1:732–5.

[10] Veenhuis RT, van Horssen J, Bos RP, et al. Highly increased urinary 1-hydroxypyrene excretion rate in patients with atopic dermatitis treated with topical coal tar. Arch Dermatol Res 2002;294:168–71.

[11] Jones SK, Mackie RM, Hole DJ, et al. Further evidence of the safety of tar in the management of psoriasis. Br J Dermatol 1985;113:97–101.

[12] Larko O, Swanbeck G. Is UVB treatment of psoriasis safe? A study of extensively UVB-treated psoriasis patients compared with a matched control group. Acta Derm Venereol 1982;62:507–12.

[13] Roelofzen JH, Aben KK, Oldenhof UT, et al. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. J Invest Dermatol 2010;130:953–61.

[14] Kiemeney LA, Sulem P, Besenbacher S, et al. A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. Nat Genet 2010;42:415–9.

[15] Hoogendoorn EH, Hermus AR, de Vegt F, et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. Clin Chem 2006;52:104–11.

[16] Bosetti C, Boffetta P, La VC. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol 2007;18:431–46.

[17] van Schooten FJ, Godschalk R. Coal tar therapy. Is it carcinogenic? Drug Saf 1996;15:374–7.

[18] Talbot-Smith A, Fritschi L, Divitini ML, et al. Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. Am J Epidemiol 2003;157:606–12.

[19] Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60: 1098–111.

[20] Brauchli YB, Jick SS, Miret M, et al. Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control analysis. J Invest Dermatol 2009;129:2604–12.

[21] Frentz G, Olsen JH. Malignant tumours and psoriasis: a follow-up study. Br J Dermatol. 1999;140:237–42.

[22] Hwang CY, Chen YJ, Lin MW, et al. Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan. Int J Cancer 2012;130:1160–7.

[23] Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, et al. Epidemiology of urinary bladder cancer: from tumor development to patient's death. World J Urol 2007;25:285–95.